

1. An implant having a tissue/implant interface, comprising  
an implant having an outer surface;  
a bioactive polymer layer adjacent to at least a portion of the outer surface; and  
controlled release nanoparticles, liposomes, or microspheres containing a tissue  
5 response modifier, wherein the controlled release nanoparticles, liposomes, or microspheres  
provides the tissue response modifier to the site of implantation in a quantity effective to  
control tissue response at the site of implantation.
2. The implant of claim 1, wherein the bioactive polymer layer is self-assembled  
with metal cations.
3. The implant of claim 2, wherein metal cations are  $\text{Fe}^{3+}$  or  $\text{Ca}^{2+}$ .
4. The implant of claim 2, wherein the self-assembled bioactive polymer layer is  
a synthetic polymer.
5. The implant of claim 2, wherein the self-assembled bioactive polymer layer is  
a mussel adhesive protein.
6. The implant of claim 2, wherein the self-assembled bioactive polymer layer is  
assembled from humic acid.
7. The implant of claim 1, wherein the bioactive polymer layer comprises  
glutamic acid.
8. The implant of claim 1, wherein the bioactive polymer layer further comprises  
covalently bound poly(ethylene oxide), phosphatidyl choline, polyvinyl alcohol, polyethylene  
imine, an adhesive ligand, or a combination thereof.

9. The implant of claim 1, wherein the bioactive polymer layer comprises a hydrogel.

10. The implant of claim 9, wherein the hydrogel is polyvinyl alcohol.

11. The implant of claim 10, wherein the hydrogel further comprises acrylic acid, humic acid, nafion, or another polymeric acids, or combinations comprising at least one of the foregoing acids.

12. The implant of claim 1, wherein the implant further comprises an additional bioactive polymer layer.

13. The implant of claim 12, wherein the additional bioactive polymer layer comprises a hydrogel.

14. The implant of claim 1, wherein the bioactive polymer layer is formed by the polymerization of 2-hydroxyethyl methacrylate, a fluorinated acrylate, acrylic acid, methacrylic acid, or a combination comprising one of the foregoing monomers with an ethylenically unsaturated co-monomer.

15. The implant of claim 1, wherein the bioactive polymer layer is formed by copolymerization of 2-hydroxyethyl methacrylate with hydroxypropyl methacrylate, N-vinyl pyrrolidinone, 2-hydroxyethyl acrylate, glycerol methacrylate, n-isopropyl acrylamide, N,N-dimethylacrylamide, glycidyl methacrylate, or a combination thereof.

16. The implant of claim 1, wherein the bioactive polymer layer is formed by copolymerization of 2-hydroxyethyl methacrylate, N-vinyl pyrrolidinone, and 2-N-ethylperfluorooctanesulfanamido ethyl acrylate in the presence of EGDMA.

17. The implant of claim 1, wherein the tissue response is inflammation, fibrosis, fibroblast formation, fibroblast function, cell proliferation, neovascularization, cell injury, cell death, leukocyte activation, leukocyte adherence, lymphocyte activation, lymphocyte adherence, macrophage activation, macrophage adherence, thrombosis, neoplasia, protein  
5 adhesion to the implant, or a combination comprising at least one of the foregoing responses.

18. The implant of claim 1, wherein the tissue response modifier comprises an anti-fibrotic agent, steroidal anti-inflammatory agent, non-steroidal anti-inflammatory agent, anti-proliferative agent, cytokine, cytokine inhibitor, growth factor, vascular growth factor, neutralizing antibody, adhesive ligand, hormone, cytotoxic agent, or a combination comprising at least one of the foregoing tissue response modifiers.

19. The implant of claim 1, comprising a tissue response modifier which affects inflammation.

20. The implant of claim 1, comprising a tissue response modifier which affects neovascularization.

21. The implant of claim 1, comprising a first tissue response modifier which affects inflammation and a second tissue response modifier which affects neovascularization.

22. The implant of claim 1, wherein the tissue response modifier comprises 2-(3-benzophenyl)propionic acid, 9-alpha-fluoro-16-alpha-methylprednisolone, methyl prednisone, fluoroxyprednisolone, 17-hydroxycorticosterone, cyclosporin, (+)-6-methoxy- $\alpha$ -methyl-2-naphthalene acetic acid, 4-isobutyl- $\alpha$ -methylphenyl acetic acid, Mitomycin C, transforming growth factor alpha, anti-transforming growth factor beta, epidermal growth factor, vascular endothelial growth factor, anti-transforming growth factor beta antibody, anti-fibroblast antibody, anti-transforming growth factor beta receptor antibody, arginine-glycine-aspartic acid, REDV, or a combination comprising at least one of the foregoing tissue response modifiers.

23. The implant of claim 1, wherein the controlled release microspheres comprise PLGA.

24. The implant of claim 1, wherein the controlled release microspheres comprise predegraded PLGA microspheres.

25. The implant of claim 1, wherein the controlled release microspheres comprise PEG-treated microspheres.

26. The implant of claim 26, wherein the controlled release microspheres comprise a mixture of standard and predegraded microspheres.

27. The implant of claim 1, wherein the controlled release microspheres further comprise PEG-treated microspheres.

28. The implant of claim 1, wherein the site of implantation is the gastrointestinal tract, biliary tract, urinary tract, genital tract, central nervous system or endocrine system.

29. The implant of claim 1, wherein the site of implantation is at blood vessels, bones, joints, tendons, nerves, muscles, the head, the neck, or organs.

30. The implant of claim 1, wherein the implant is a material, a prostheses, an artificial organ, a repair device, an implantable drug delivery system, or a biosensor.

31. A controlled release delivery system, comprising a mixture of predegraded and untreated microspheres.

32. The controlled release delivery system of claim 31, wherein the microspheres comprise PLGA.

33. The controlled release delivery system of claim 31, wherein predegraded microspheres are made by stirring standard microspheres in a solvent for a time sufficient to produce a rough surface of the microsphere.

5 34. The controlled release delivery system of claim 31, further comprising PEG-treated microspheres.

10 35. The controlled release delivery system of claim 31, wherein the tissue response modifier comprises an anti-fibrotic agent, steroidal anti-inflammatory agent, non-steroidal anti-inflammatory agent, anti-proliferative agent, cytokine, cytokine inhibitor, growth factor, vascular growth factor, neutralizing antibody, adhesive ligand, hormone, cytotoxic agent, or a combination comprising at least one of the foregoing tissue response modifiers.

36. The controlled release delivery system of claim 31, wherein the tissue response modifier comprises 2-(3-benzophenyl)propionic acid, 9- $\alpha$ -fluoro-16- $\alpha$ -methylprednisolone, methyl prednisone, fluoroxyprednisolone, 17-hydroxycorticosterone ,  
5 cyclosporin, (+)-6-methoxy- $\alpha$ -methyl-2-naphthalene acetic acid, 4-isobutyl- $\alpha$ -methylphenyl acetic acid, Mitomycin C, transforming growth factor alpha, anti-transforming growth factor beta, epidermal growth factor, vascular endothelial growth factor, anti-transforming growth factor beta antibody, anti-fibroblast antibody, anti-transforming growth factor beta receptor antibody, arginine-glycine-aspartic acid, REDV, or a combination comprising at least one of  
10 the foregoing tissue response modifiers.

37. A tissue/implant interface comprising the controlled release delivery system of claim 31.